Remarks / Arguments

Claims 27-43 are pending in this application. Claims 1-26 and 44 have been cancelled previously.

Claim 27 has been amended to clarify that 1) the sheet of diffusion-controlling matrix has dimensions which are sufficient to permit bringing material to be detected into contact with spatially-discrete areas of the sheet, and 2) the spatial distribution of signals produced in the sheet of diffusion-controlling matrix is to be detected relative to the sheet of matrix.

The present claims relate to a system for obtaining an image of the location(s) of one or more signals indicative of the presence of one or more substances to be detected, which substances are located at different positions relative to one another. This system includes a "sensor layer", which is a sheet of diffusion-controlling matrix material which contains one or more biological sensor materials (bioluminescent cells with reporter gene constructs) suspended throughout. It also includes appropriate means for detecting the location of the signals produced by the sensor material in response to the presence of substance(s) to be detected. In operation, substance(s) to be detected is/are brought into contact with the sensor layer at discrete locations on the sensor layer, they diffuse into the sensor layer and contact the bioluminescent cells with reporter gene constructs which in turn produce signals at the positions on the sensor layer where the substances to be detected are in contact with the sensor layer. These signals are finally detected, providing the locations on the sensor layer which are in contact with the substance(s) to be detected.

The sensor layer of the present claims allows large-scale detection of the biological activity of substances brought into contact with it. In other words, it can be used for activity imaging purposes. Thus, the locally varied release and distribution of active ingredients in, for example, plant parts or animal tissues can be imaged directly on the basis of their biological activities. In practice, the sensor layer provides relatively high resolutions, making it possible for fine structures of the activity distribution to be imaged in detail.

Claims 27-29, 31-39, and 41-43 stand rejected as obvious over Simpson '643 in view of Thastrup '021. The examiner states that "it would be have been obvious to one of ordinary skill in the art for the cells of Thastrup et al to be encapsulated in a polymer matrix, as suggested by Simpson et al, in order to provide the cells with a greater degree of protection and allow for long term application of the biosensor". This conclusion makes no sense.

Thastrup describes a process which allows the measurement of the modulating activity of substances on the intracellular localization of specific proteins of signaling pathways. For this purpose, genetically modified cells which express a luminophore, such as for example variants of the Green Fluorescent Protein (GFP) are used. GFP is fused with the corresponding target proteins to form corresponding hybrid proteins. In the Thastrup process the expression and the intracellular localization and distribution of these hybrid proteins can be recorded by fluorescence measurement by means of fluorescence microscopy and CCD cameras.

In other words, in Thastrup the spatial distribution of luminescence in suitably modified living cells is detected to monitor intracellular translocation of cellular components in response to something which "influences" the cells, to study modulation of intracellular pathways. The cells themselves are the object of study. The goal is to determine how the cells react in response to the material being used to influence them. The goal is not to employ the cells to determine the location of the material which influences the cells to produce signal(s). The Thastrup process is fundamentally not capable of providing information on the distribution of biological activity on a macro scale, such as for example on the surface of objects. As the examiner recognizes, the cells are not present in a sheet of diffusion-controlling matrix.

By contrast, in the system defined by the present claims, the bioluminescent cells are employed in a macro-scale sheet of diffusion-controlling matrix (sensor layer) as sources of signals which indicate the presence and location of materials which possess biological activity detectable by the bioluminescent cells, and which are in contact with this sensor layer. The spatial distribution of the signals is relative to the sensor layer, not the cells themselves. The cells themselves are not the object of study.

Simpson '643 describes an OASIC (optical application specific integrated circuit), a monolithic bioelectronic device which contains a bioluminescent bioreporter (bioluminescent cells), located in a selectively permeable "container" which is suitably affixed to the OASIC. The OASIC is a miniaturized unit with deliberately confined geometric dimensions. An OASIC of this type is generally used in miniaturized low cost sensors, typically intended for employment in hostile environments.

The "container" of the OASIC of Simpson differs from the sensor layer described in the present application both from the point of view of its structure and its utility. The OASIC is a miniaturized unit, while the sensor layer of the present claims allows generally unlimited dimensions, a dimension of 20 x 20 cm having proved to be successful for routine use. The OASIC can only conduct spotwise measurements at the places in its environment where the OASIC is employed, while the present sensor layer produces site-dependent, quasicontinuous signals over the entire detection area.

In support of his conclusion of obviousness, the examiner states, "Simpson et al., however, teach a biosensor comprising bioreporters enclosed in polymer matrix (column 7, lines 65-67). Simpson et al specifically teach encapsulated cells that can be formed into sheets or thickness or diameter desired, where cells may be added to molten agar or agarose, where gelation occurs as the agar or agarose cools to room temperature (column 68, lines 33-51). Simpson et al further teach that the polymer matrix provides the cells with a greater degree of protection (column 6, lines 45-55, and also teach that encapsulation allows for long term application of the biosensor (column 68, lines 5-20)."

Simpson at column 68, lines 32-41 states "The deposition of microbial organisms on integrated circuits may be accomplished through the various protocols described below. The ultimate goal of these encapsulation methods is to provide the cells with a stable microenvironment limited from the stresses of their outer environment. Encapsulated cells can be formed into sheets or beads, almost of any thickness or diameter desired, depending on the

method chosen. The small area available for cell deposition on an integrated circuit requires thin sheets (0.1-2 mm) or small diameter beads (< 50 μm) to be produced."

The above-quoted text of Simpson makes it clear that Simpson teaches that the encapsulated cells can be formed into sheets of almost any thickness, or beads of almost any diameter desired, but that as the integrated circuit has only a small area available for cell deposition, the sheets should be thin (0.1-2 mm) or the beads should be small diameter (< 50 μm). However, the examiner states that Simpson et al. "teach encapsulated cells that can be formed into sheets or thickness or diameter desired..." The examiner appears to be attempting to interpret the Simpson language as teaching that the encapsulated cells of Simpson can be formed into sheets of any desired size. There is nothing in Simpson which teaches or suggests this. Simpson requires that any sheets of encapsulated cells must be thin and of small dimensions to fit onto an integrated circuit.

Regarding the examiner's statements about the polymer matrix providing the cells with a greater degree of protection (column 6, lines 45-55)(erroneous reference) and that encapsulation allows for long term application of the biosensor (column 68, lines 5-20), the applicants respond that protection from the environment of Simpson's intended use and relatively long-term utility of the detector are valid considerations for Simpson's probe, which is intended for use in "hostile" environments, but these factors are not relevant to study of the bioluminescent cells of Thastrup.

The issue presented by the rejection here is whether the cells of Thastrup should be encased in a polymer matrix, and if so, whether that polymer matrix should be formed in the shape of a sheet. There is no reason for the Thastrup cells to be located in a polymer matrix of any shape, sheet or otherwise. First, they don't need protection as they are not being employed as part of a probe and do not need to be held in contact with the detector as in Simpson. Secondly, there is no reason to believe that the Thastrup cells would function any longer or better in a polymer matrix than in the presumably quite suitable medium employed by Thastrup in his studies. Furthermore, there is absolutely no suggestion that the cells of Thastrup should be

encased in a sheet of polymer matrix. Thastrup is concerned with individual cells. Placing the cells in a sheet of matrix would serve no purpose in Thastrup's process.

In his section entitled "Response to Arguments", the examiner states in the first paragraph of section 16 that suspending the cells in a matrix would not negate the utility of the device of Thastrup et al., and the advantages of suspending the cells as discussed above would in fact provide motivation for modifying the invention of Thastrup et al. The applicants have already responded to this argument above.

In the second paragraph of section 16, the examiner states that the applicants have argued that Thastrup et al do not teach bring(ing) any substance into contact with any spatially discrete area of the sheet of the Simpson reporter material. The undersigned does not see such an argument in his previous response, but agrees with the statement. The examiner continues, stating that "Thastrup et al do teach contacting cells with a substance and determining the spatial distribution or change in the spatial distribution of cell luminescence. Since the cells are part of the sheet of diffusion-controlling matrix, the substance would by default have to come into contact with spatially discrete areas of the sheet." The applicants respond that the examiner's statement regarding Thastrup's contacting cells with a substance and determining the spatial distribution or change in the spatial distribution of cell luminescence is correct, but the second part of the examiner's statement is incorrect. The cells of Thastrup are not part of a sheet of diffusion-controlling matrix. It is in the Simpson reference that the bioluminescent cells are encased in a polymer layer, and in Simpson, any substance to be detected must necessarily come into contact with the entire surface of the polymer layer, not just with a spatially-discrete area of it. Neither Thastrup nor Simpson teaches or suggests bringing a substance to be detected into contact with a spatially-discrete area of a matrix layer containing bioluminescent cells.

Applicants reiterate that the dependent claims of this application should be patentable as proper dependent claims of a patentable head claim if and when the head claim 27 is found to be

patentable. Therefore, it is not necessary to respond in detail to the examiner's numerous rejections of the dependent claims.

In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

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